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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,809	04/13/2006	Avi Avramoff	30825	5244

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EXAMINER	
WESTERBERG, NISSA M	
ART UNIT	PAPER NUMBER
1618	

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03/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,809	AVRAMOFF ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1 - 6, 8, 10 - 16, 18, 20, 21, 24, 25, 50 - 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 - 32, 34, 36 - 42, 44, 46, 47, 49, 58, 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1 - 6, 8, 10 - 16, 18, 20, 21, 24 - 32, 34, 36 - 42, 44, 46, 47, 49 - 59.

DETAILED ACTION

Applicants' arguments, filed December 22, 2008, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Response to Arguments

1. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection presented below.

Claim Rejections - 35 USC § 112 – 1st Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26 – 32, 34, 36 – 42, 44, 46, 47, 49, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Applicant does not have support for

formulations in which lansoprazole is the "sole active ingredient". The various formulations prepared contain lansoprazole but also contain other ingredients which are active ingredients. The subcoating layer of the dosage form contains an alkaline agent, which is an active substance in that it alters or controls the pH of the formulation. The examples prepared also contain other pharmaceutically active ingredients. The formulation in example 5 contains the surface active agent sodium lauryl sulfate, which is used in the treatment of varicose veins. The lactose present in the substrate and subcoating layer of example 1 is pharmaceutically active as a nutrient which provides carbohydrates. Therefore, Applicant does not have support for administering a therapeutically effective amount of lansoprazole as sole active ingredient.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 26 – 32, 34, 36 – 40, 42, 44, 46, 47, 49, 50, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Depui et al. (WO 96/24375) in view of Lundberg (EP 1174136) and Edgren et al. (US 6,210,712).

WO'375 discloses an oral, enteric coated dosage form comprising an acid labile proton pump inhibitor useful in the treatment of disorders associated with *Heliobacter* infections (abstract). In examples 5 (beginning of p 28) and 12 (beginning on page 39), a multilayer dosage form comprising lansoprazole (in the free base form, not as a pharmaceutically acceptable salt) is prepared. The core contains a sugar sphere seed (neutral core) coated with lansoprazole, the cellulosic polymer hydroxypropyl methyl cellulose (HPMC) and water (aqueous solvent). No alkaline material is present in the core. The size of the core can vary between 0.1 – 2 mm (p 13, ln 13 – 14). The separating layer (subcoating layer of the instant claims) comprises the cellulosic

polymer hydroxypropyl cellulose, the filler talc, magnesium stearate and the solvent water. An enteric coating layer comprising a methacrylic acid copolymer and the plasticizer triethyl citrate (a citric acid ester) is present in the dosage form. The active ingredient can be mixed with other ingredients such as binders, surfactants and fillers (p 13, ln 18 – 26). In example 18 (beginning on page 46), the surfactant sodium lauryl sulfate and the filler anhydrous lactose are included in the same layer as the active benzimidazole ingredient (omeprazole).

WO'375 does not disclose the use of sodium stearate or a surfactant such as polysorbate 80 or sodium lauryl sulfate in the subcoating layer.

Lundberg et al. discloses similar trilayer (active ingredient core, intermediate layer and enteric layer) dosage form containing proton pump inhibitor compounds. In example 1 (beginning on p 9), a separating layer comprising talc (filler), sodium dodecyl sulfate (surfactant, also know as sodium lauryl sulfate), microcrystalline cellulose (cellulosic polymer) and magnesium stearate (alkaline agent) is added. These ingredients are mixed with granulated active ingredient and no solvent is present. No other pharmaceutically active substances are present in the dosage form. Disclosed pharmaceutically acceptable surfactants include non-ionic and ionic surfactants such as sodium lauryl sulfate or polysorbates (¶ [0032]).

Edgren et al. discloses that potassium stearate, magnesium stearate and sodium stearate as pharmaceutically acceptable lubricants (col 8, ln 6 – 10).

It would have been obvious to one of ordinary skill in the art to prepare a multi-layer dosage form as disclosed by WO'375 and to use sodium stearate and a surfactant

such as polysorbate 80 or sodium lauryl sulfate in the subcoating layer. Claim 26, subitem (b) uses the transitional phrase "consisting essentially". Applicant has argued that "consisting essentially of" excludes all other components such as, additional active ingredients, which would add to the cost and complexity of manufacture of the instant invention. Because of the use of the completely open transitional phrase "comprising" in the preamble and the absence of a clear indication in the specification or claims, the transitional phrase "consisting essentially of" is still being interpreted as comprising (emphasis added, see p 9 of the Office Action mailed June 23, 2008 for more information).

WO '375 discloses that surfactants can be included in the dosage form and Lundberg discloses that polysorbate 80 or sodium lauryl sulfate are surfactants suitable for inclusion in the subcoating layer of trilayer, benzimidazole proton pump inhibitor containing dosage forms. Selection of excipients for a dosage form is part of routine formulation and optimization by one of ordinary skill in the art, based on the cost, availability of various excipients and the interactions which may occur between the different excipients and the other ingredients in both the subcoating layer and adjacent layers of the oral lansoprazole dosage form.

The composition of WO'375 contains both a benzimidazole proton pump inhibitor such as lansoprazole and an antibiotic while the compositions disclosed by Lundberg only contain a benzimidazole proton pump inhibitor. Thus, Lundberg teaches the presence of an antibacterial compound in a proton pump dosage form is not required. In maintenance therapy where control of stomach acidity by the proton pump inhibitor is

desired but the bacterial infection has been treated, a dosage form with only lansoprazole would be appropriate to reduce the chances of an antibacterial resistant strain of bacteria developing.

The person of ordinary skill in the art would have been motivated to use sodium stearate and reasonably would have expected success because WO'375 teaches that magnesium stearate can be used in subcoating layer and Edgren et al. discloses that magnesium stearate and sodium stearate are functionally equivalent, as they are both lubricants. Applicant has argued that magnesium stearate and sodium stearate are not functionally equivalent because the instant invention uses sodium stearate not as a lubricant but as an alkaline agent. An alkaline agent must be water soluble and magnesium stearate is not water soluble and so is not an alkaline agent and is known to be stronger than sodium stearate. The Examiner is unaware of any definition of an alkaline agent that requires the compound to be soluble in water, but rather that the acidic or basic nature of a compound is determined the by the concentration of hydrogen ions present in a solution. Evidence for the stated definition of alkaline agent is requested. Applicant also appears to contradict the assertion that magnesium stearate is not an alkaline agent on p 17, ¶ 5 of the Response filed December 22, 2008, that states "Also, sodium stearate is known to be weaker than magnesium stearate, while both alkaline agents are weak alkaline agents, such that using the weakest member of an already weak group of alkaline agents would not be expected to have the desired effect..." (emphasis added). The properties of a compound are inseparable from the compound itself. Therefore, while sodium stearate may be labeled as an alkaline

agent in the instant invention, it is also acting as a lubricant. Therefore, the functional equivalence of magnesium and sodium stearate as lubricants taught Edgren renders the substitution of sodium stearate into the formulations of WO'375 obvious to one of ordinary skill in the art.

8. Claims 26 – 32, 34, 36 – 42, 44, 46, 47, 49, 50, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Depui WO'375, Lundberg and Edgren et al. as applied to claims 26 – 32, 34, 36 – 40, 42, 44, 46, 47, 49, 50, 58 and 59 above, and further in view of Napper et al. (US 2002/0150618).

WO'375, Lundberg and Edgren et al. discloses a lansoprazole dosage form with an active substrate center that does not contain an alkaline substance; a subcoating layer containing sodium stearate, a cellulosic polymer such as HPMC, a filler, polysorbate 80 or sodium lauryl sulfate as the surfactant and a solvent; and an enteric coating.

Depui WO'375 discloses the use of anhydrous lactose as a filler material but not the use of lactose monohydrate.

Napper et al. discloses that either lactose monohydrate or anhydrous lactose are suitable directly compressible pharmaceutically acceptable excipients (¶ [0016]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use lactose monohydrate in the lansoprazole containing pharmaceutical composition taught by Depui WO'375, Lundberg and Edgren et al. The person of ordinary skill in the art would have been motivated to make those

modifications and reasonably would have expected success because Napper et al. teaches that lactose monohydrate and anhydrous lactose are functionally equivalent as excipients and one of ordinary skill would select the appropriate material based on availability of the different hydrate forms and any moisture demands of the pharmaceutical formulation process.

9. Claims 26 – 32, 34, 36, 38 – 42, 44, 46, 47, 49, 50, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Depui et al. (US 2002/0155153) in view of Lundberg (EP 1174136) and Edgren et al. (US 6,210,712).

In example 4 (¶ [0109]) of Depui '153, enteric coated tablets of lansoprazole are prepared. These dosage forms are administered one to several times a day to treat gastrointestinal side effects caused by NSAIDs (non-steroidal anti-inflammatory drugs; ¶ [0087]). The core consists of non-pareil cores coated with water, the surfactant sodium lauryl sulfate, lansoprazole and the cellulosic polymer HPMC. A separating (subcoating) layer comprised of water and ethanol as solvents, the filler talc, the surfactant polyethylene glycol 6000 (PEG 6000) and the cellulosic polymer HPMC is applied. Then an enteric coating of hydroxypropoly methylcellulose phthalate, the plasticizers acetyltributyl citrate and cetanol (cetyl alcohol) is applied to the pellets.

The separating layer may serve as a diffusion barrier and pH-buffering zone (¶ [0062]). To strengthen the buffering capacity of this layer, substance such as the inorganic salts generally used as antacids (for example, aluminum or calcium hydroxide, carbonate or silicate; or magnesium oxide, carbonate or silicate), weak inorganic acids

such as citric acid or suitable organic bases such as the basic amino acids are added (¶ [0062]).

The enteric coating layer can be comprised of a number of materials, including methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate phthalate and cellulose acetate trimellitate (¶ [0064]). The enteric layer may also contain pharmaceutically acceptable plasticizers such as citric acid esters, phthalic acid esters, cetyl alcohol and polysorbates (¶ [0065]).

Depui '153 does not explicitly disclose a lansoprazole preparation in which an inorganic or organic basic salt is present in the separating layer, or the inclusion of sodium stearate, polysorbate 80 and/or sodium lauryl sulfate in the subcoating layer.

Lundberg et al. discloses similar trilayer (active ingredient core, intermediate layer and enteric layer) dosage form containing proton pump inhibitor compounds. In example 1 (beginning on p 9), a separating layer comprising talc (filler), sodium dodecyl sulfate (surfactant), microcrystalline cellulose (cellulosic polymer) and magnesium stearate (alkaline agent) is added. These ingredients are mixed with granulated active ingredient and no solvent is present. No other pharmaceutically active substances are present in the dosage form. Disclosed pharmaceutically acceptable surfactants include non-ionic and ionic surfactants such as sodium lauryl sulfate or polysorbates (¶ [0032]).

Edgren et al. discloses that potassium stearate, magnesium stearate and sodium stearate are functionally equivalent (col 8, ln 6 – 10).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a multilayer lansoprazole oral dosage for administration as taught by US'153 and to include an alkaline agent, such as a basic amino acid or calcium carbonate in the separating layer, as the inclusion of such compounds in the separating layer is taught to improve the pH-buffering capacity of this layer, It also would be obvious to include a polysorbate or sodium lauryl sulfate surfactant in the subcoating layer, taught as suitable for inclusion in the separating layer by Lundberg. The examples of Depui '153 contain magnesium stearate, which is taught as functionally equivalent to sodium stearate by Edgren et al. Applicant has argued that magnesium stearate and sodium stearate are not functionally equivalent because the instant invention uses sodium stearate not as a lubricant but as an alkaline agent. An alkaline agent must be water soluble and magnesium stearate is not water soluble and therefore it is not an alkaline agent and is known to be stronger than sodium stearate. The Examiner is unaware of any definition of an alkaline agent that requires the compound to be soluble in water, but rather that the acidic or basic nature of a compound is determine the by the concentration of hydrogen ions present in a solution. Evidence for the stated definition of alkaline agent is requested. Applicant also appears to contradict the assertion that magnesium stearate is not an alkaline agent on p 17, ¶ 5 of the Response filed December 22, 2008, that states "Also, sodium stearate is known to be weaker than magnesium stearate, while both alkaline agents are weak alkaline agents, such that using the weakest member of an already weak group of alkaline agents would not be expected to have the desired effect..." (emphasis added). The

properties of a compound are inseparable from the compound itself. Therefore, while sodium stearate may be labeled as an alkaline agent in the instant invention, it is also acting as a lubricant. Therefore, the functional equivalence of magnesium and sodium stearate as lubricants taught Edgren renders the substitution of sodium stearate into the formulations of WO'375 obvious to one of ordinary skill in the art.

Claim 26, subitem (b) uses the transitional phrase "consisting essentially". Applicant has argued that "consisting essentially of" excludes all other components such as, additional active ingredients, which would add to the cost and complexity of manufacture of the instant invention. Because of the use of the completely open transitional phrase "comprising" in the preamble and the absence of a clear indication in the specification or claims, the transitional phrase "consisting essentially of" is still being interpreted as comprising (emphasis added, see p 9 of the Office Action mailed June 23, 2008 for more information).

10. Claims 26 – 32, 34, 36 – 42, 44, 46, 47, 49, 50, 58 and 59 rejected under 35 U.S.C. 103(a) as being unpatentable over Depui '153, Lundberg and Edgren et al. as applied to claims 26 – 32, 34, 36, 38 – 42, 44, 46, 47, 49, 50, 58 and 59 above, and further in view of Depui et al. (WO 96/24375) and Napper et al. (US 2002/0155153).

Depui '153, Lundberg and Napper et al. teaches a lansoprazole dosage form with an active substrate center that does not contain an alkaline substance; a subcoating layer containing sodium stearate, a cellulosic polymer such as HPMC, a filler,

polysorbate 80 or sodium lauryl sulfate as the surfactant and a solvent; and an enteric coating.

None of the references discloses the use of lactose as a filler material in the layer with the lansoprazole.

WO '375 discloses that anhydrous lactose can be present in the core material (substrate) of multi-layered benzimidazole proton pump inhibitor dosage (e.g., example 18 on p 46).

Napper et al. discloses that either lactose monohydrate or anhydrous lactose are suitable directly compressible pharmaceutically acceptable excipients (¶ [0016]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use lactose monohydrate in the lansoprazole containing pharmaceutical composition taught by Depui '153, Lundberg and Edgren et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Depui '375 teaches that anhydrous lactose can included in the substrate layer and Napper et al. teaches that lactose monohydrate and anhydrous lactose are functionally equivalent as excipients and one of ordinary skill would select the appropriate material based on availability of the different hydrate forms and any moisture demands of the pharmaceutical formulation process.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW